Paper No. 31

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JACK D. BURTON and
DAVID M. GOLDENBERG

Appeal No. 2003-0177
Application No. 09/231,642

HEARD: April 15, 2003

Before WILLIAM F. SMITH, SCHEINER, and LORIN, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1 through 6, 8, 9, and 13 through 22. Claims 7 and 10 through 12 are pending but have been withdrawn from consideration by the examiner. Claims 1, 4, 5, 6, and 9 are representative of the subject matter on appeal and read as follows:

1. A targeting moiety comprising a conjugate of an antibody linked to a ligand-binding region of interleukin-13 receptor α subunit (IL-12Rα), which antibody is specific for a cellular antigen specific to a targeted cell.

4. A targeting moiety as claimed in claim 1, comprising a bispecific antibody that has a first specificity for a cellular antigen specific to a targeted cell and a second specificity for IL-13Rα receptor subunit.

5. A targeting moiety as claimed in claim 1, wherein the antibody is specific to an antigen expressed by solid tumors and is linked to the ligand-binding region of IL-12Rα.

6. A targeting moiety as claimed in claim 5, wherein the antibody is specific to carcinoembryonic antigen.

9. A kit comprising a conjugate of interleukin-12 (IL-13) linked to a drug, radionuclide or toxin, and a targeting moiety comprising an antibody specific for a cellular antigen specific to a targeted cell, linked to the ligand-binding region of interleukin-13 receptor α subunit (IL-13Rα).

The references relied upon by the examiner are:

Hansen et al. (Hansen)	5,874,540	Feb. 23, 1999
PCT Application (Eshhar)	WO 93/19163	Sep. 30, 1993
PCT Application (Willson)	WO 97/15663	May 1, 1997

MacLean et al. (MacLean), "Anti-CD3:Anti-IL-2 Receptor-Bispecific mAb-Mediated Immunomodulation," Journal of Immunology, Vol. 155, pp. 3674-3682 (1995)

Claims 1 through 3, 5, 6, 8, 9, and 13 through 21 stand rejected under 35 U.S.C. § 103(a). As evidence of obviousness, the examiner relies upon Eshhar, Willson, and Hansen. Claims 1, 4, and 22 also stand rejected under 35 U.S.C. § 103(a) with the examiner relying upon MacLean in addition to Eshhar, Willson, and Hansen. We reverse.

Discussion

Initially, we need to clarify what subject matter has been examined and thus before us for review. As seen, claim 1 is directed to a targeting moiety which comprises a conjugate having two portions. The first portion is an antibody and the second portion is a ligand-binding region of interleukin-13 receptor α subunit (IL-13Rα). The antibody is specific for a cellular antigen specific to a targeted cell. However, as a result of a

restriction requirement, claim 1 has only been examined to the extent that the antibody is specific to carcinoembryonic antigen (CEA). See Paper No. 8, page 3 ("The claims encompass non-elected embodiments. These claims will be examined only to the extent they read on a targeting moiety comprising an antibody specific to CEA linked to a ligand binding region of IL-13Rα."). Thus, it appears that claim 6 reflects the subject matter which has been examined by the examiner on the merits and thus before us for review in this appeal.

Eshhar describes a conjugate which also comprises an antibody and a ligand-binding region of a cellular receptor. Specifically, the antibody portion of the Eshhar conjugate is a single-chain Fv domain (scFv) of a specific antibody. Eshhar, page 7, lines 9-16. A preferred embodiment of Eshhar is that the conjugate is to target tumor cells and the scFv domain is derived from an antibody specific to an epitope expressed on the tumor cell. Id., page 19, lines 7-9. There is no dispute on this record that CEA would have been an obvious choice to one of ordinary skill in the art in designing the conjugate of Eshhar to target tumor cells. As set forth by appellants:

> CEA is a glycosylated cell surface protein of approximately 180 kDa, and is a solid tumor antigen that has been extensively studied clinically, both as a circulating tumor marker and as an antigenic target for radiolabeled mAbs for imaging and therapy. A number of anti-CEA antibodies have been under study in phase I-III clinical diagnostic and therapeutic trials. Exemplary of an anti-CEA mAb is the MN-14mAb. A humanized version of this mAb, hMN-14, in which human constant and framework regions replace the corresponding mouse sequences, has been constructed and expressed and is the mAb and used in these clinical trials. A ^{99m}Tc-labeled Fab' fragment of another, related anti-CEA mAb, Immu-4, has received FDA approval for the detection and staging of colon cancer.

Specification, page 19, lines 9-24.[1] Thus, for the purposes of this appeal, the issue becomes whether it would have been obvious to one of ordinary skill in the art to use IL-13Rα as the receptor portion of the Eshhar conjugate. We agree with appellants that it would not have been obvious to do so from the references relied upon by the examiner.

We initially note that the examiner's position is difficult to review due to the manner in which the Examiner's Answer was crafted. The examiner refers the reader of the Answer to Paper Nos. 8 and 13 for a statement of the two rejections pending in this appeal. This is manifestly improper. As set forth in the Manual of Patent Examining Procedure § 1208, "[o]nly those statements of grounds of rejection appearing in a single prior action may be incorporated by reference. An examiner's answer should not refer, either directly or indirectly, to more than one prior Office action." The examiner's error is exacerbated in this appeal because Paper No. 13 refers the reader to Paper No. 8. In reviewing Paper 8, we believe we understand the examiner's position on the merits
sufficiently to conclude that the references relied upon by the examiner, at least in the manner applied by the examiner, do not support a prima facie case of obviousness.

The receptor portion of the Eshhar conjugate must function as a "lymphocyte-triggering molecule." Eshhar, page 7, lines 27-35. To this end, a chimeric gene encoding the Eshhar conjugate is used to transfect T-cells or other lymphocytes so that the "scFv linked to receptor subunits [will] serve to transduce the signal from the scFv and confer antibody specificity to T cells as well as other lymphocytes." Eshhar, page

[1] The examiner relies upon Hansen to establish the obviousness of this aspect of the claimed conjugate. In view of appellants' admissions, we need not dwell on Hansen.

16, lines 27-31. Candidate molecules for the receptor portion of the Eshhar conjugate are "receptor molecules which take part in signal transduction as an essential component of a receptor complex, such as receptors which trigger T cells and NK activation and/or proliferation." Eshhar, page 17, lines 5-8.

Given this disclosure in Eshhar, it was the examiner's responsibility to establish by factual evidence that IL-13Rα is a receptor which meets the signal transducing requirements of Eshhar. The statement of the rejection in Paper No. 8 does not discuss this issue in any manner. Rather, this issue was developed through appellants' arguments over the course of the prosecution of this application. This points out the danger in the examiner referring to a statement of rejection appearing earlier in the prosecution instead of ensuring that the statement of rejection appearing in the Examiner's Answer is up to date and complete and reflects the amendments to the claims and arguments presented by applicant in the course of the prosecution.

The examiner belatedly attempted to recapture this lost ground by responding to the arguments set forth in applicants' Appeal Brief. The examiner states at page 5 of the Examiner's Answer that Willson teaches that IL-13Rα is a "high affinity receptor capable of signal transduction," citing to page 27, lines 8-10 of the reference. The phrase "signal transduction" does in fact appear at that portion of Willson. However, appellants responded to the examiner's belated position stating:

> [T]he examiner has identified no teaching in Eshhar or elsewhere that IL-13Rα is involved in signal transduction to any of the cells identified by Eshhar, i.e., in signalling the cell bearing the chimera to generate a cellular response directed toward the specific antigen encoded by the chimera in a MHC nonrestricted manner (see Eshhar at page 8. lines 21-24). To the contrary, Willson teaches that IL-13R is produced by activated T-cells, but acts on macrophages to induce differentiation and suppress the production of inflammatory cytokines. In other words, the

> signal transduction production of inflammatory cytokines. In other words, the signal transduction mentioned on page 27 of Willson entails the signalling of cells such as macrophages, and does not involved signalling of the T-cells themselves as in Eshhar. Thus, there is no basis for substituting the ligand binding region of IL-13Rα for the ligand binding region of IL-2Rα in Eshhar.

Reply Brief, paragraph bridging pages 2-3.

The examiner did not file a substantive response to the Reply Brief. Thus, we have no basis to disagree with appellants' position that the "signal transduction" of Willson differs from the "signal transduction" required by Eshhar. Absent a fact -based explanation from the examiner establishing that the "signal transduction" of Willson is in fact the "signal transduction" envisioned by Eshhar, the rejection cannot be sustained.

As we understand the examiner's rejection of claims 1, 4, and 22, MacLean is relied upon only to show the bispecific antibody required by claim 4 on appeal and is not relied upon to show the overall conjugate required by claim 1. We do not find that MacLean makes up for the shortcomings of the examiner's rejection premised upon Eshhar and Willson. Thus, we also reverse this rejection.

Other Issues

As explained above, the conjugate of claim 1 is broadly directed in part to an antibody specific for a cellular antigen specific to a targeted cell. However, claim 1 has only been examined to the extent that the antibody is specific to CEA. As result of the action we have taken today, the claims on appeal are free of rejection. Upon return of the application to the examiner, the examiner and appellants should carefully consider the broad scope of claim 1 on appeal in light of the disclosure at page 7 of Willson describing conjugates of IL-13Rα and immunoglobulins which allow targeting of the conjugate to particular cells.[2] These conjugates may anticipate claim 1 in its broadest sense.

Also upon return of the application, the examiner and appellants should review all of the claims pending to ensure that they are in proper form. For example, claims 16 and 14 may be considered duplicates. Also, the examiner rejected claim 4 and claim 22 which depends from claim 4 separately, presumably because of the requirement of claim 4 for a bispecific antibody. However, claims 16 and 19 also appear to be directed to bispecific antibodies yet were not separately rejected by the examiner. It is not clear from this record whether this was an oversight on the part of the examiner or whether the examiner is reading claims 16 and 19 in a manner different from claim 4. Further, the examiner and appellants should focus on the specific language used in the dependent claims to make sure it is appropriate. For example, it is not clear from claim 4 as presently drafted whether the bispecific antibody is a third portion of the conjugate

[2] We note as did the examiner that the nomenclature "NR4" appearing at this portion of Willson is stated at page 1 of the reference to be interchangeable with IL-13Rα.

of claim 1 or whether the bispecific antibody of claim 4 is a further limitation on the antibody required by claim 1. If the latter is intended by appellants, claim 4 should be redrafted using language such as "wherein the antibody is a bispecific antibody . . .." See, e.g., claim 5 on appeal.

The decision of the examiner is reversed.

REVERSED

William F. Smith Administrative Patent Judge	)
Toni R. Scheiner Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
Hubert C. Lorin Administrative Patent Judge	)

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